

CLAIMS

1. A method of determining whether a patient has, or is responding to treatment for, cystic fibrosis the method comprising the steps of (1) obtaining a suitable epithelial cell sample from the patient, (2) determining whether nucleotide diphosphate kinase (NDPK) function or state is altered compared to its function or state in a control epithelial cell.
2. A method according to Claim 1 wherein phosphorylation of NDPK is altered.
3. A method according to Claim 1 wherein nucleoside triphosphate production from a given nucleoside diphosphate is measured.
4. A method of determining whether a patient has, or is responding to treatment for, cystic fibrosis the method comprising the steps of (1) obtaining a suitable epithelial cell sample from the patient, (2) determining whether histidine phosphorylation of annexin is altered compared to its phosphorylation in a control epithelial cell.
5. A method according to Claim 4 wherein the histidine is His246 or His293 of annexin.
6. A method according to any one of Claims 1 to 5 wherein the epithelial cell sample from the patient is a lung cell sample or a nasal cell sample.

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7. A method of classifying a disease state associated with epithelial cell dysfunction in a patient, the method comprising (1) obtaining a suitable epithelial cell sample from the patient and (2) determining for one or more of the following whether the measured parameter is altered compared to a control epithelial cell the measured parameters being: (i) nucleoside diphosphate kinase (NDPK) function, (ii) phosphorylation of annexin, (iii) phosphorylation of other membrane proteins, and (iv) ATPase activity.

8. A method according to Claim 7 wherein in step (ii) phosphorylation of annexin at His246 or His293 is measured.

9. A method according to Claim 7 wherein each of parameters (i) and (ii) are measured in the sample from the patient and compared to the control sample.

10. A method according to Claim 7 wherein each of parameters (i), (ii) and (iii) are measured in the sample from the patient and compared to the control sample.

11. A method according to Claim 7 wherein all of parameters (i) to (iv) are measured in the sample from the patient and compared to the control sample.

12. A method according to any one of Claims 7 to 11 wherein the epithelial cell sample from the patient is a lung cell sample or a nasal cell sample.

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13. A method according any one of Claims 7 to 12 wherein the effectiveness of a treatment for cystic fibrosis is being tested on the patient.

5 14. A method of identifying a compound useful in treating cystic fibrosis or which may aid the identification of a compound useful in treating cystic fibrosis the method comprising identifying a compound which modulates or restores nucleoside diphosphate kinase activity.

10 15. A method according to Claim 14 wherein phosphorylation of NDPK is altered.

15 16. A method according to Claim 14 wherein nucleoside triphosphate production from a given nucleoside diphosphate is altered.

20 17. A method of identifying a compound useful in treating cystic fibrosis or which may aid the identification of a compound useful in treating cystic fibrosis the method comprising identifying a compound which modulates histidine phosphorylation of annexin.

18. A method according to Claim 17 wherein the histidine phosphorylation of annexin is at His246 or His293.

25 19. A method of identifying a compound useful in treating cystic fibrosis or which may aid the identification of a compound useful in treating cystic fibrosis the method comprising identifying a compound which modulates the interaction between any of cystic

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fibrosis transmembrane conductance regulator protein (CFTR), nucleoside diphosphate kinase (NDPK) and annexin.

Sub B4 } 5 20. A method according to any one of Claims 14 to 19 wherein the method is carried out *in vivo*.

10 21. A method of identifying a compound useful in treating cystic fibrosis or which may aid identification of a compound useful in treating cystic fibrosis the method comprising identifying a compound which substantially changes one or more of the following parameters from the state found in a cystic fibrosis epithelial cell to the state found in a normal cell, namely (i) nucleoside diphosphate kinase (NDPK) function, (ii) phosphorylation of annexin, (iii) phosphorylation of other 15 membrane proteins such as p11 and p116, and (iv) ATPase activity.

22. A method according to Claim 21 wherein the histidine phosphorylation of annexin is at His246 or His293.

Sub B5 } 20 23. A compound identified by the method of any one of Claims 14 to 22.

24. A compound according to Claim 23 for use in medicine.

25 25. A method of treating CF the method comprising administering to a patient a compound which modulates nucleoside diphosphate kinase activity or a compound which modulates histidine phosphorylation of annexin or a compound which modulates the interaction between

any of cystic fibrosis transmembrane conductance regulator protein (CFTR), nucleoside diphosphate kinase (NDPK) and annexin.

26. A method according to Claim 25 wherein the histidine phosphorylation of annexin is at His246 or His293.

27. Use of a compound as defined in Claim 36 in the manufacture of a medicament for treating cystic fibrosis.

28. A peptide of relative molecular mass less than 6500 comprising at least ten consecutive amino acid residues surrounding the phenylalanine 508, or at least ten consecutive residues including a portion of the region between residues 508 and 551, in the polypeptide sequence of human cystic fibrosis transmembrane regulator (CFTR), or a variant or precursor thereof.

29. A peptide according to Claim 28 having between 12 and 50 amino acid residues.

30. A peptide according to Claim 29 having between 12 and 30 amino acid residues.

31. A peptide according to Claim 30 having between 12 and 20 amino acid residues.

32. A peptide according to any one of Claims 28 to 31 which has the sequence KENIIFGVSYDEYR.

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33. A peptide according to any one of Claims 28 to 32 further comprising a lipid-solubilising moiety.

34. A peptide according to Claim 33 wherein the lipid-solubilising moiety is a lipid.

35. A peptide according to Claim 33 wherein the lipid-solubilising moiety is a cholesterol.

36. A peptide according to Claims 33 or 34 wherein the lipid-solubilising moiety is a fatty acid.

37. A peptide according to Claim 36 where in the fatty acid is any one of palmitic or myristic acid.

38. A peptide according to any one of Claims 28 to 37 for use in medicine.

39. A pharmaceutical formulation comprising a peptide according to any one of Claims 28 to 37 and a pharmaceutically acceptable carrier.

40. A method of treating cystic fibrosis or a chronic sputum producing disorder the method comprising administering to the patient an effective amount of a peptide according to any one of Claims 28 to 37.

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41. A method according to Claim 40 wherein the peptide is administered in a nebulised form.

42. Use of a peptide according to any one of Claims 28 to 37 in the manufacture of a medicament for treating cystic fibrosis or a chronic sputum producing disorder.

43. A peptide of relative molecular mass less than 6500 comprising at least five consecutive residues surrounding histidine 246 of annexin.

44. A peptide of relative molecular mass less than 6500 comprising at least five consecutive residues surrounding histidine 293 of annexin.

45. A peptide according to Claim 43 or 44 wherein the said histidine residue is phosphorylated.

46. A method of raising an antibody reactive with histidine phosphorylated annexin, the method comprising using a peptide according to Claim 45 as an immunogen.

47. A method according to Claim 46 wherein the said peptide is combined with a carrier or adjuvant or both.

48. An antibody obtainable by the method of Claim 46 or 47.

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49. An antibody reactive against annexin phosphorylated at histidine 246 but not reactive against annexin not phosphorylated at histidine 246.
- 5 50. An antibody reactive against annexin phosphorylated at histidine 293 but not reactive against annexin not phosphorylated at histidine 293.

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